

Follicle development

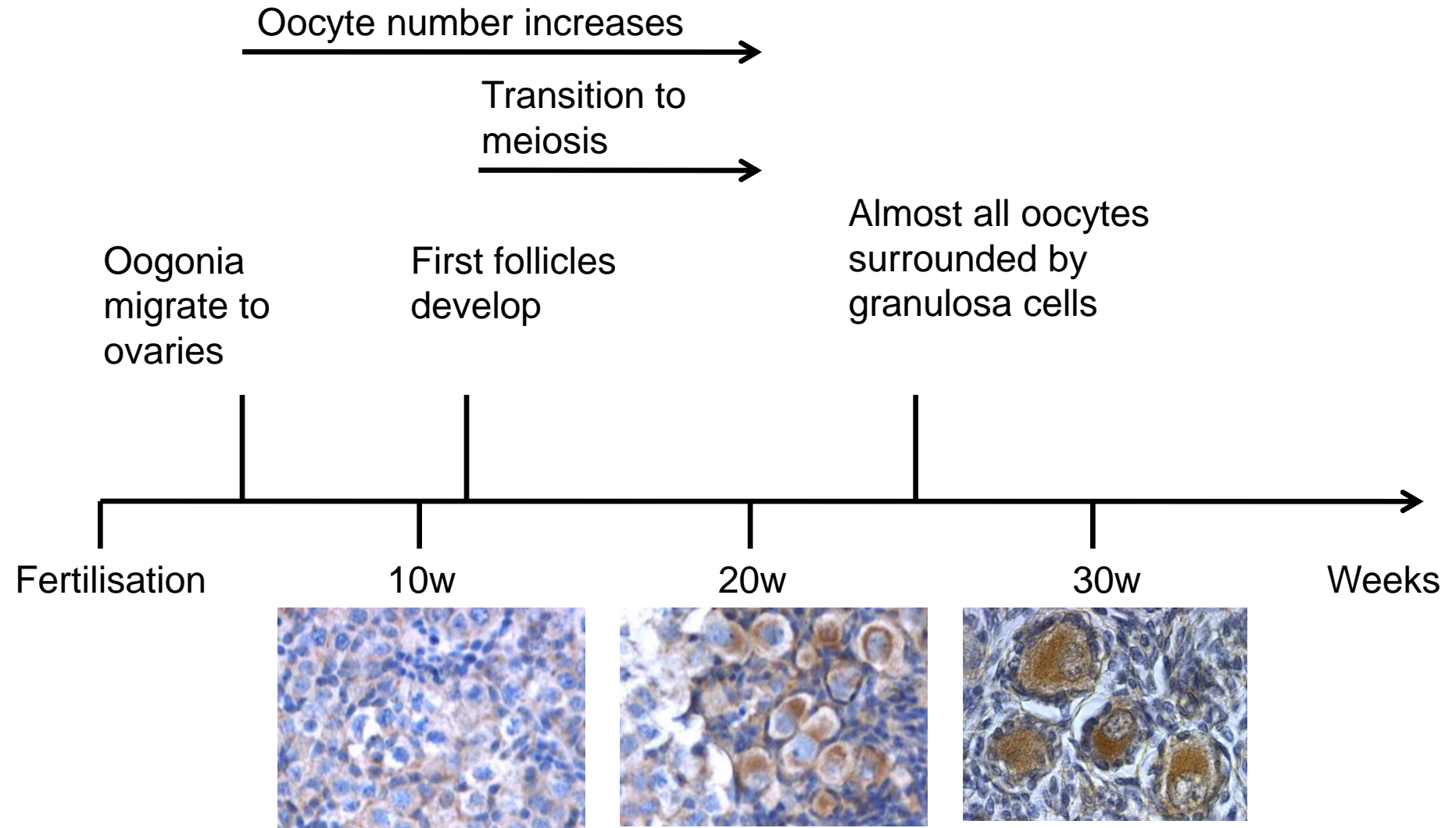
Juha Tapanainen

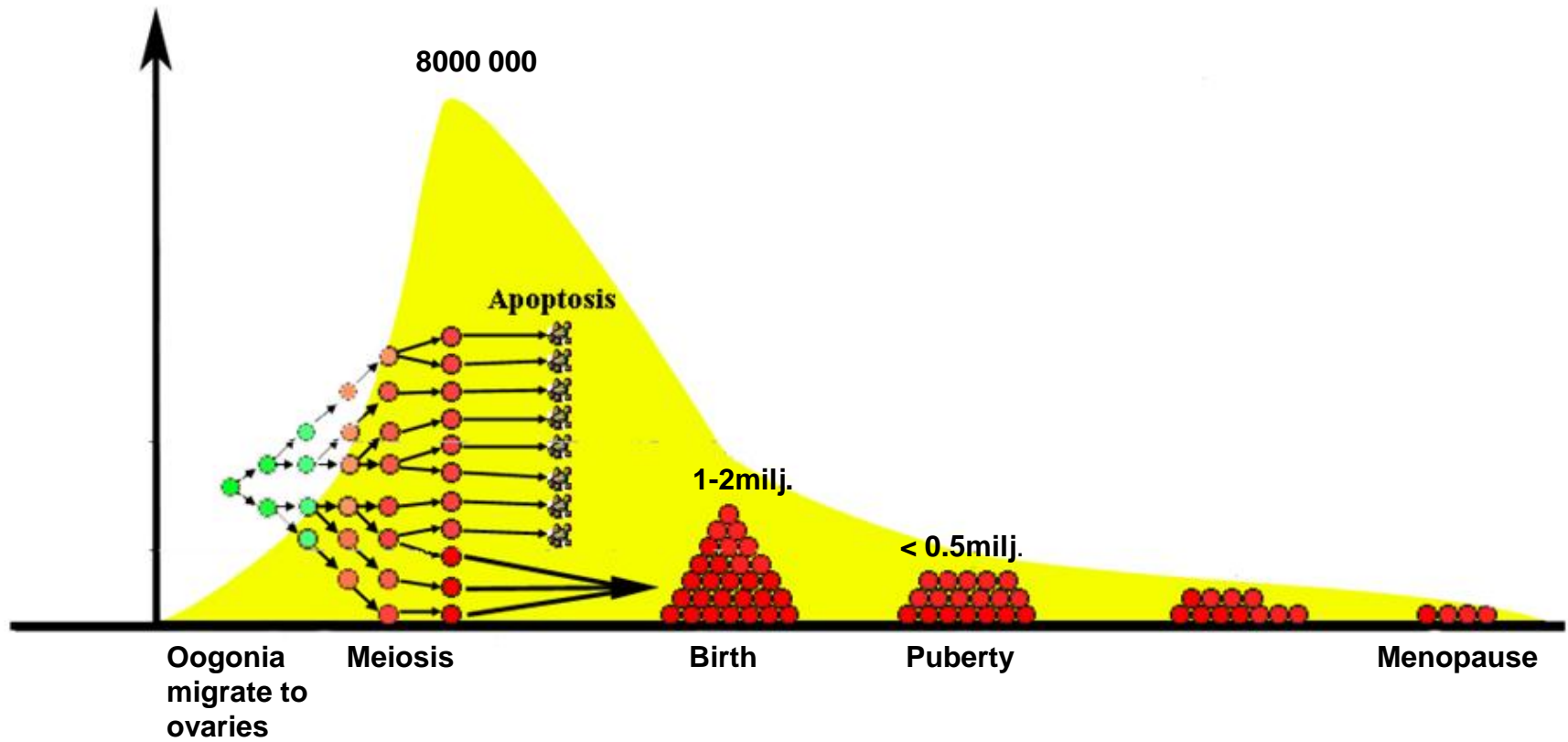
Reproduktioendokrinologia
Helsinki 7.2.2013

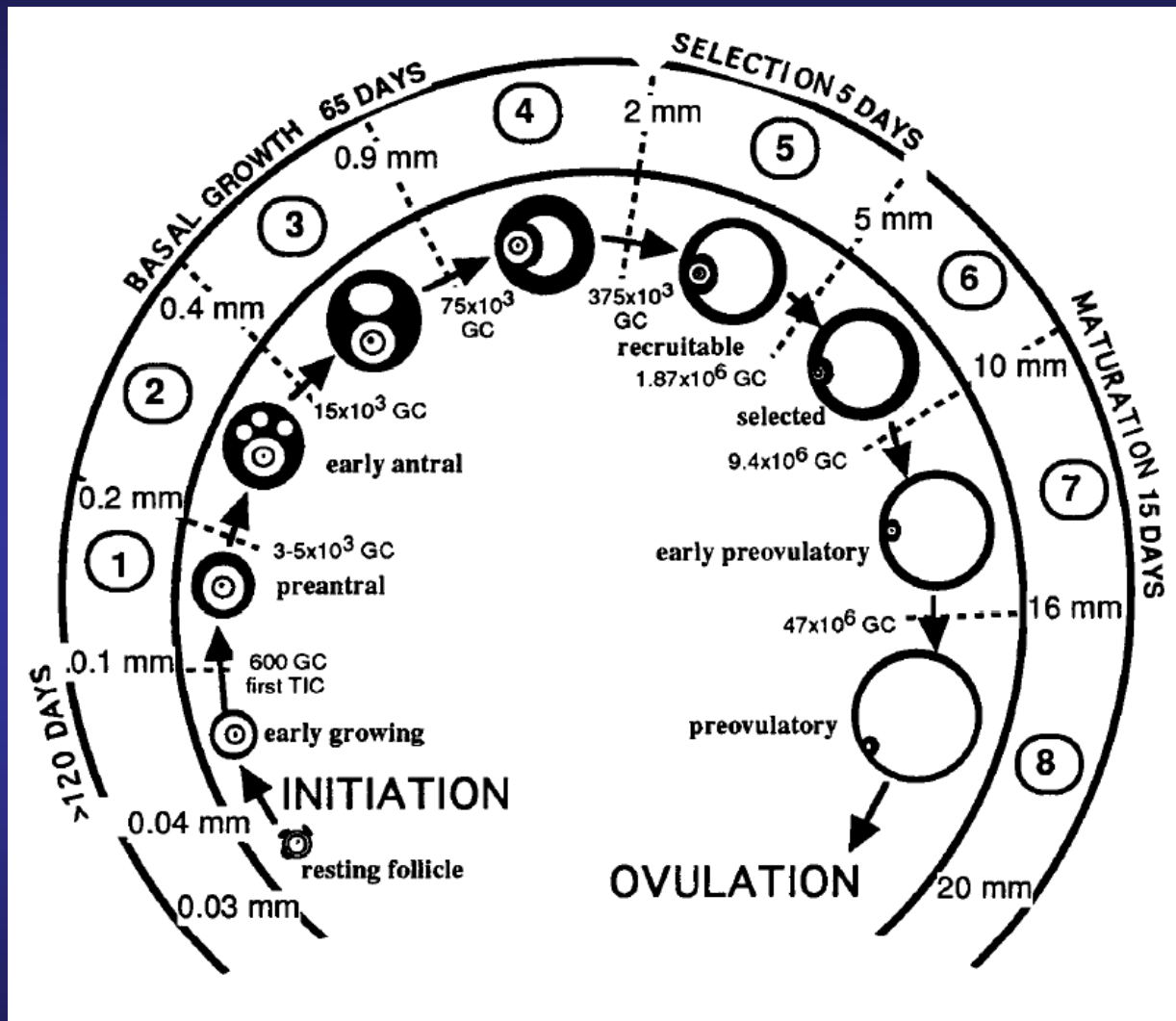
Objectives

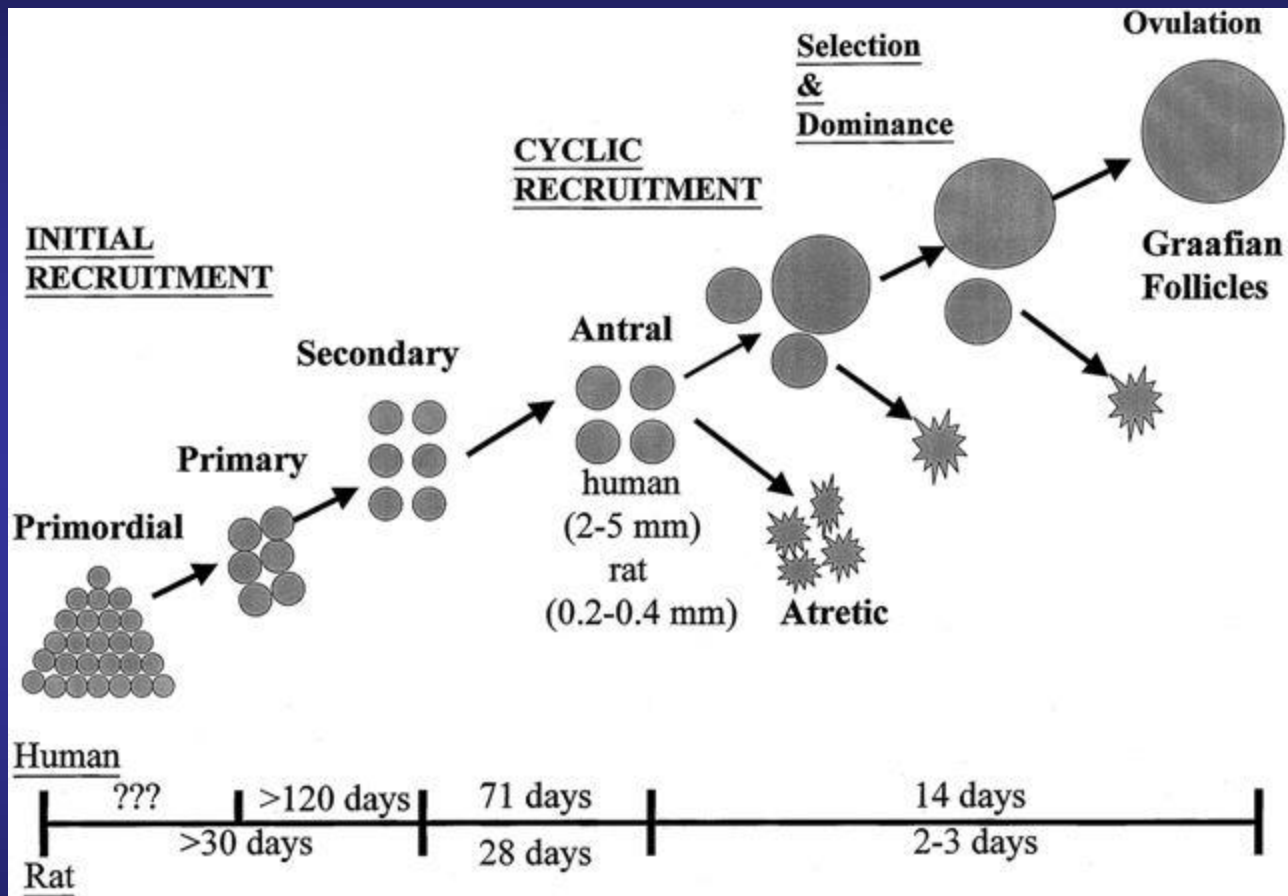
- Follicular development and gonadotropin independent and dependent phases of follicular growth
- What can be learned from gonadotropin/receptor mutations in human
- What can be learned from gonadotropin/receptor knockout models
- Follicle recruitment and dominance
- Intraovarian modulators of follicular development
- Ovulation

Ovarian Development







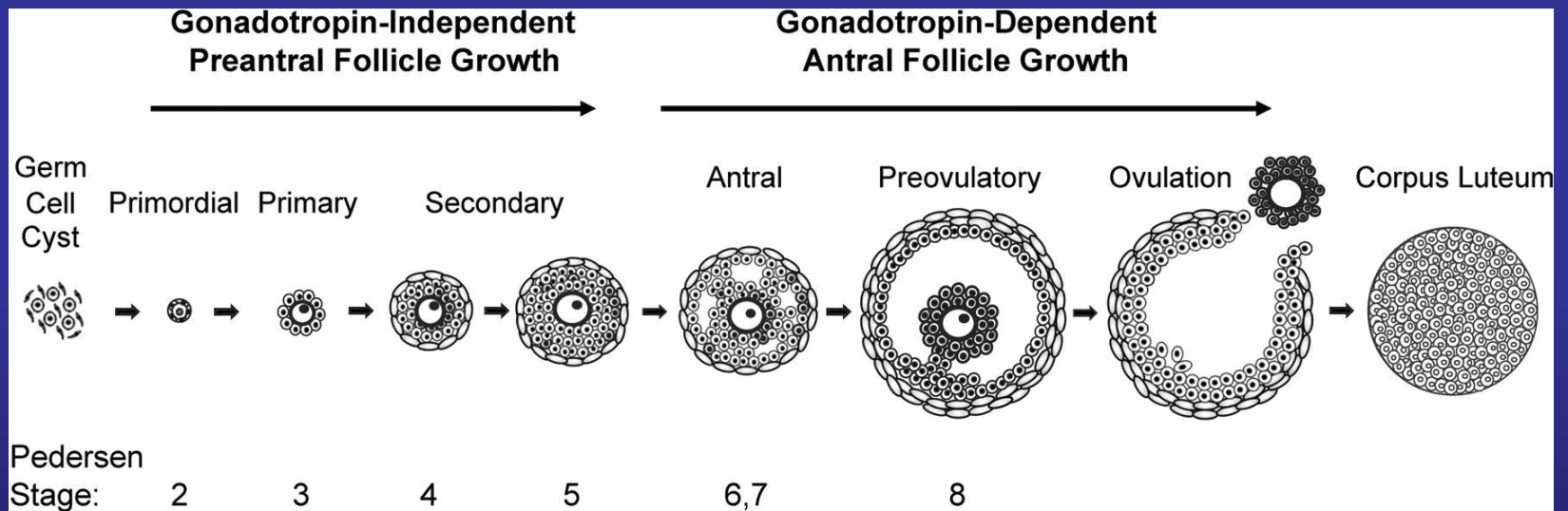


Follicular development

- Initial follicle development
- FSH-dependent progression
- LH-responsive maturation

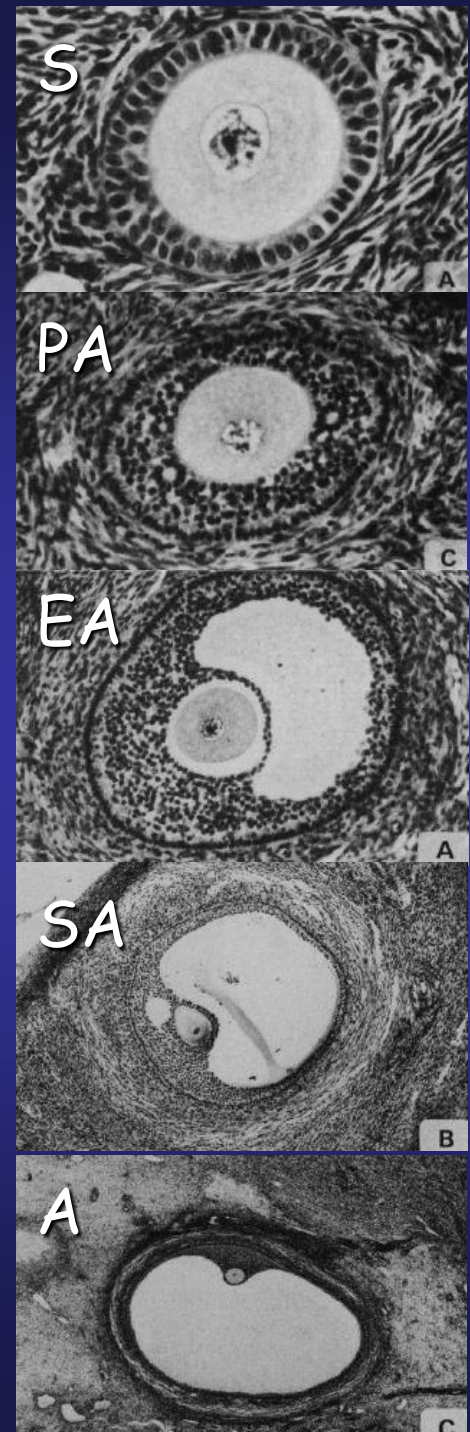
Hillier 2001

Follicle growth



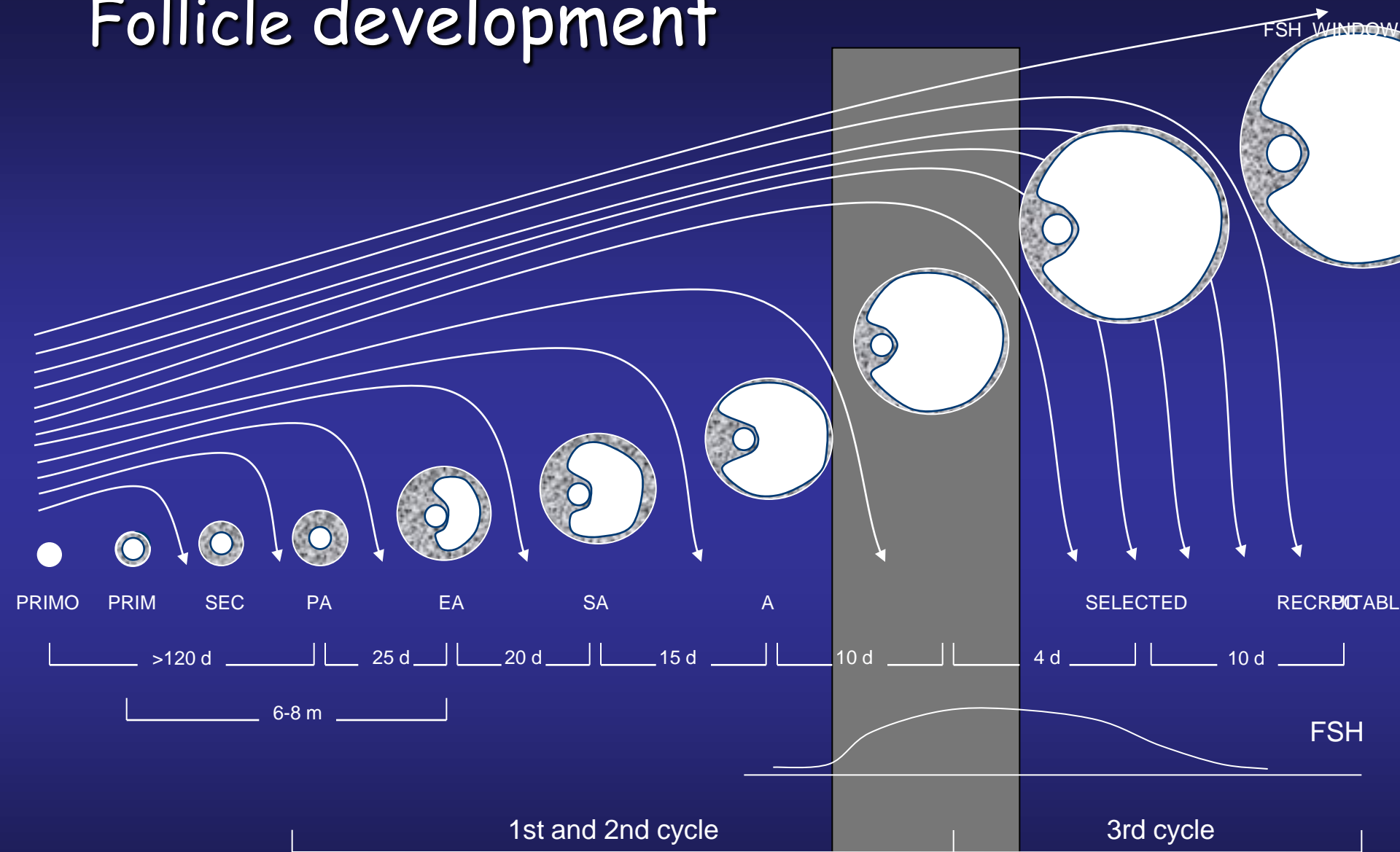
Classification of follicles

- **Secondary**: distinct TC layer, blood supply
- **Preamtral**: several gc layers
- **Early antral**: fluid-filled patchy appear within GC
- **Small antral**
- **Antral**: large crescent-shaped cavity
- **Graafian**: 15-25 mm



From Gougeon 1996

Follicle development



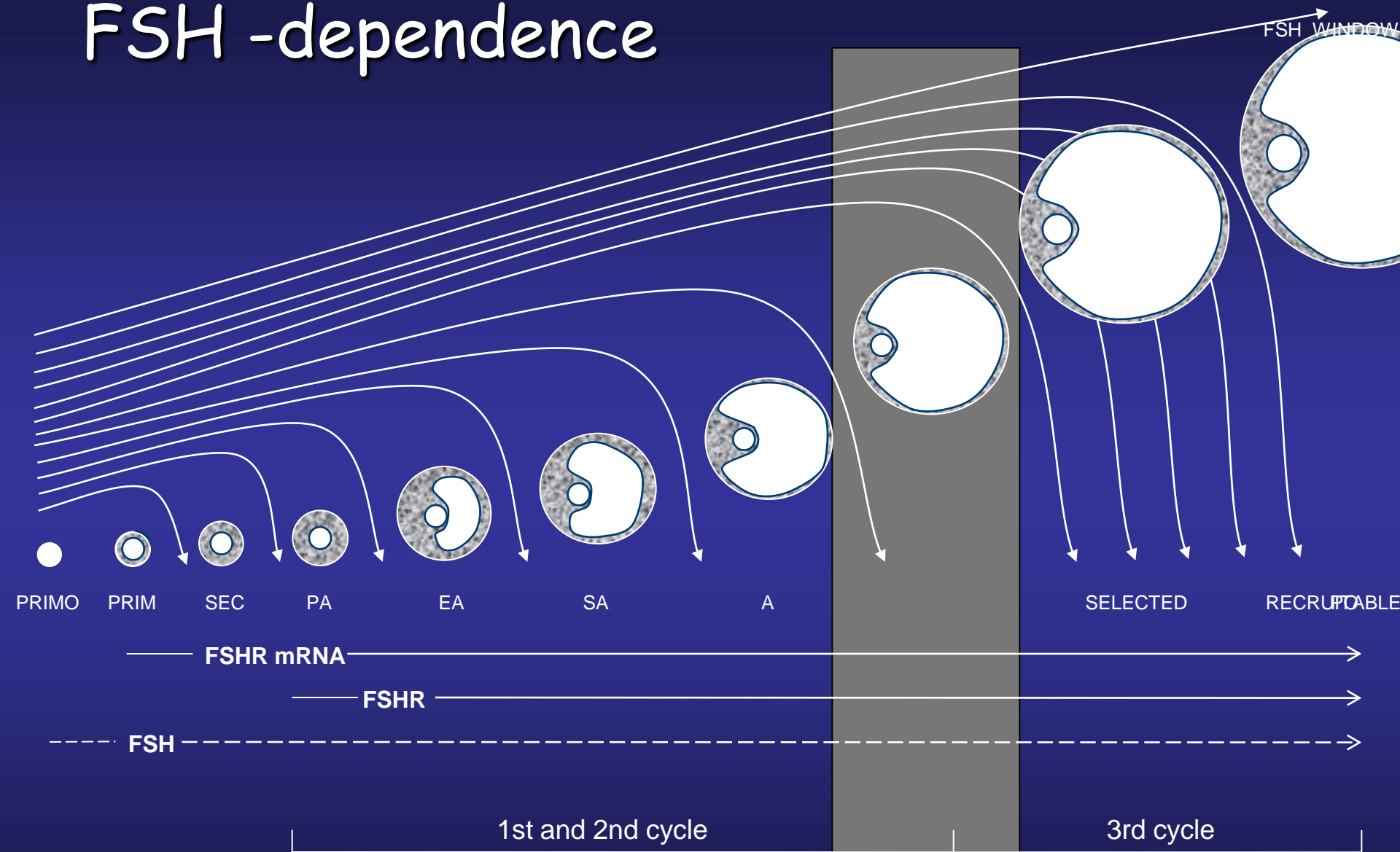
Oocytes

- Fetus 7×10^6
- Newborn 1×10^6
- Puberty 4×10^5
 - Ovulation 300-400
- Menopause 100-1000

= 99.9% of oocytes die by
the mechanism of apoptosis



FSH -dependence



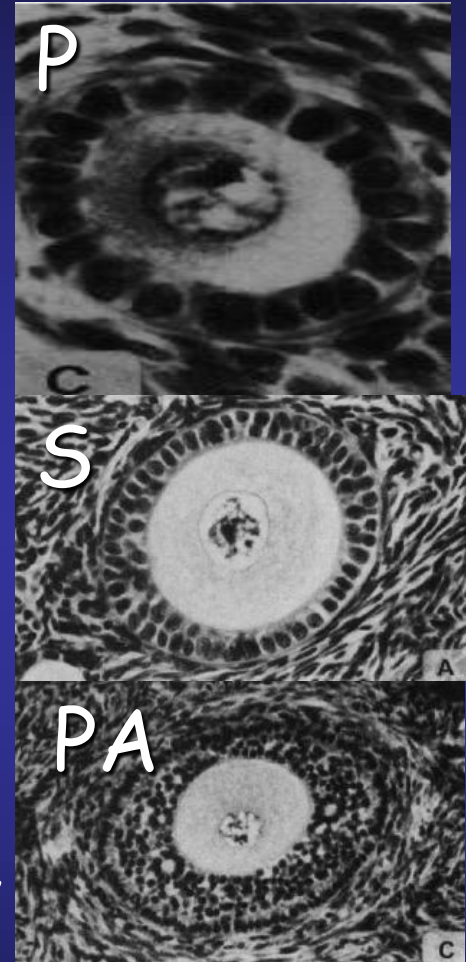
FSH-dependence

- FSHR mRNA - primary onwards

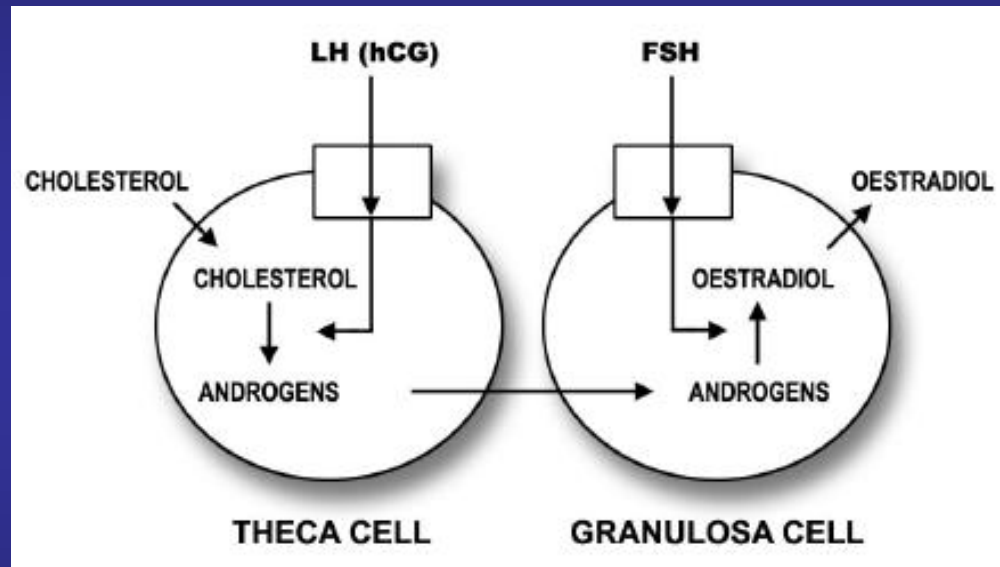
» Human

- FSHR - early preantral follicles

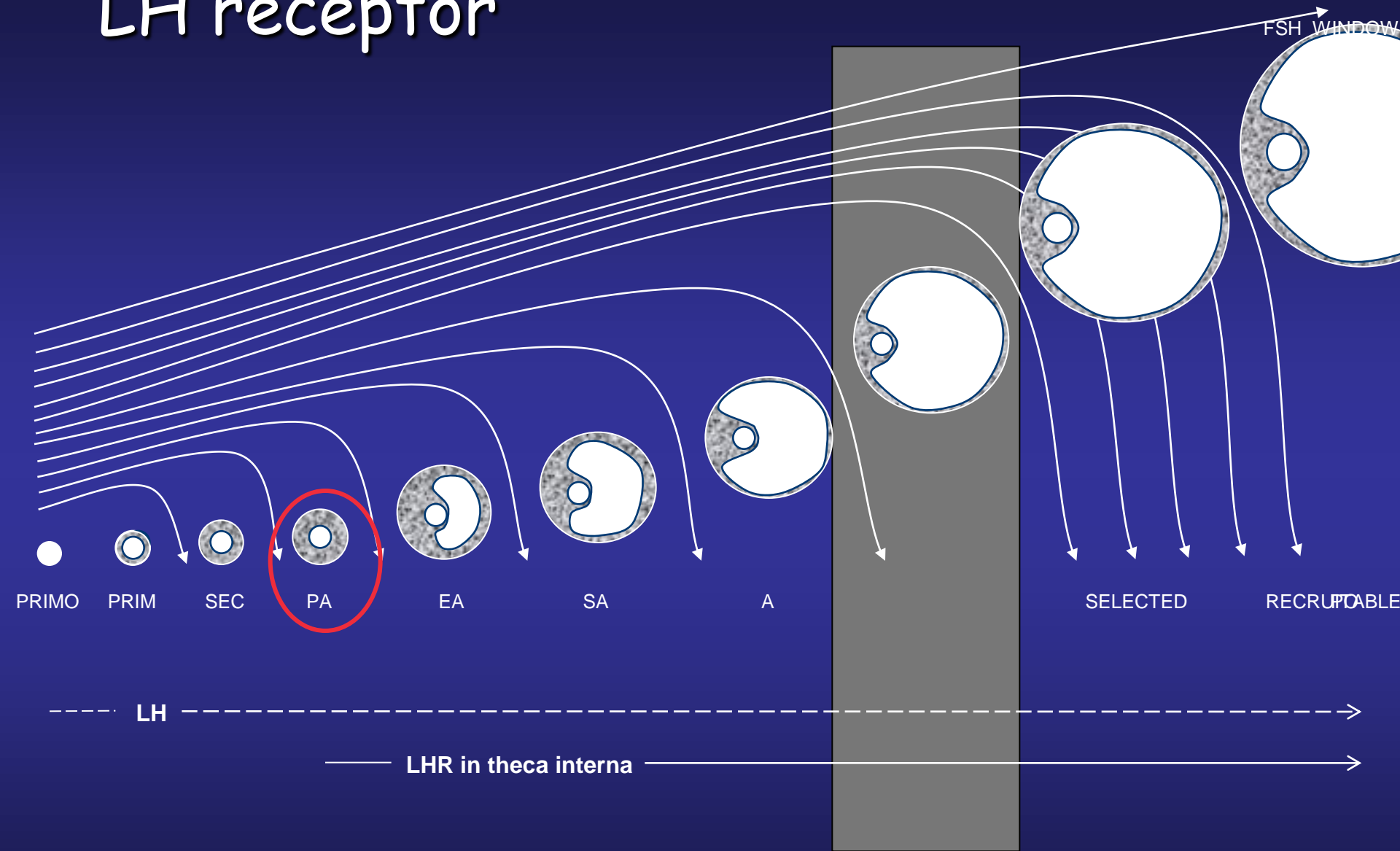
» Channing & Kammerman 1973,
Roy et al. 1987



Follicle growth and steroidogenesis



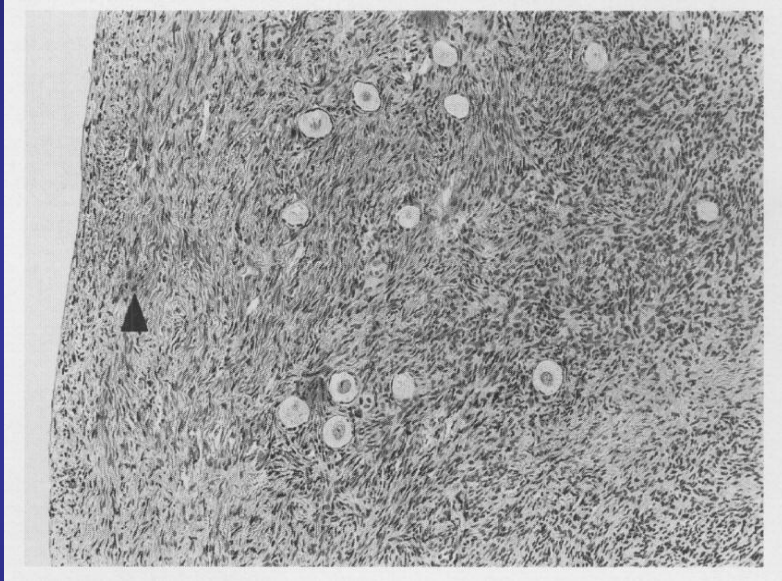
LH receptor



Gonadotropin/receptor mutations in human

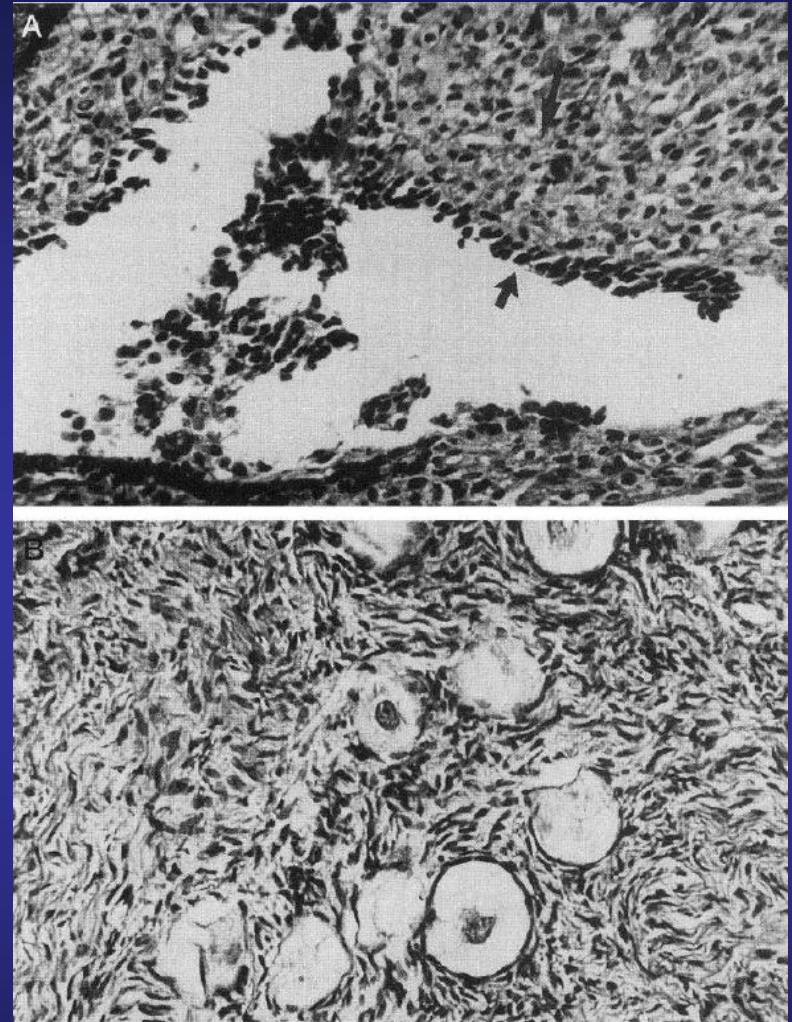
- Inactivating FSH β
 - Layman et al. 1997, 2002; Matthews et al. 1993
- Inactivating FSHR
 - Aittomäki et al. 1995; Beau et al. 1998; Touraine et al. 1999
- Activating FSHR (ligand hCG)
 - Smits et al. 2003; Vasseur et al. 2003
- Inactivating LHR
 - See Themmen & Huhtaniemi 2000

Inactivating FSHR



Aittomäki et al. 1995

Inactivating LHR



Toledo et al. 1996

Gonadotropin/receptor knockout (KO) mice

- FSH β - no follicles beyond preantral stage
 - » Kumar et al. 1997
- FSHR - follicles up to secondary stage
 - » Dierich et al. 1998; Abel et al. 2000
- LH β - degenerating antral follicles, no CL
 - » Ma et al. 2004
- LHR - no follicles beyond antral stage
 - » Lei et al. 2001; Zhang et al. 2001, Pakarainen et al. 2005



Normal



FSHRKO



FSH beta



LuRKO

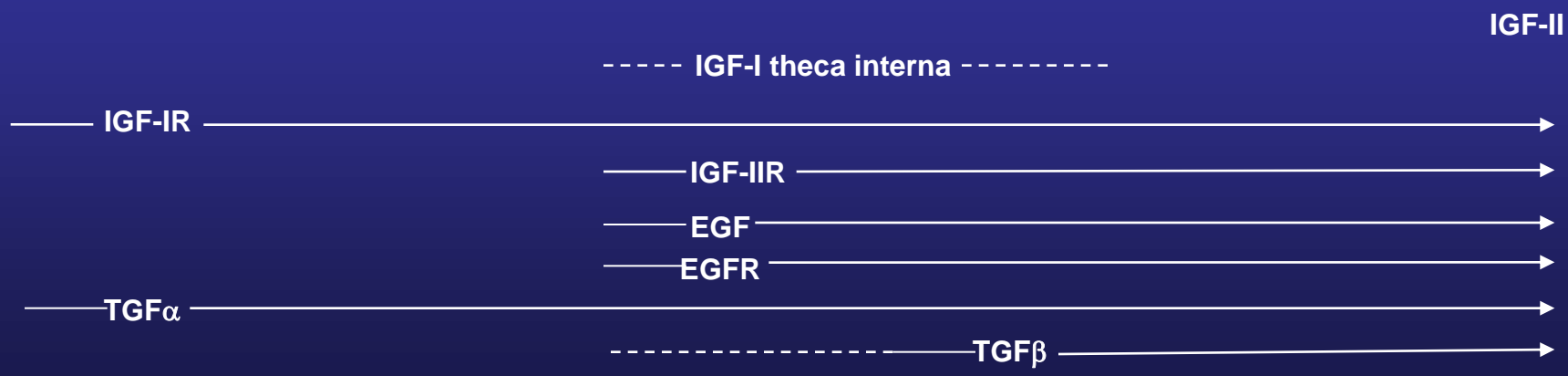
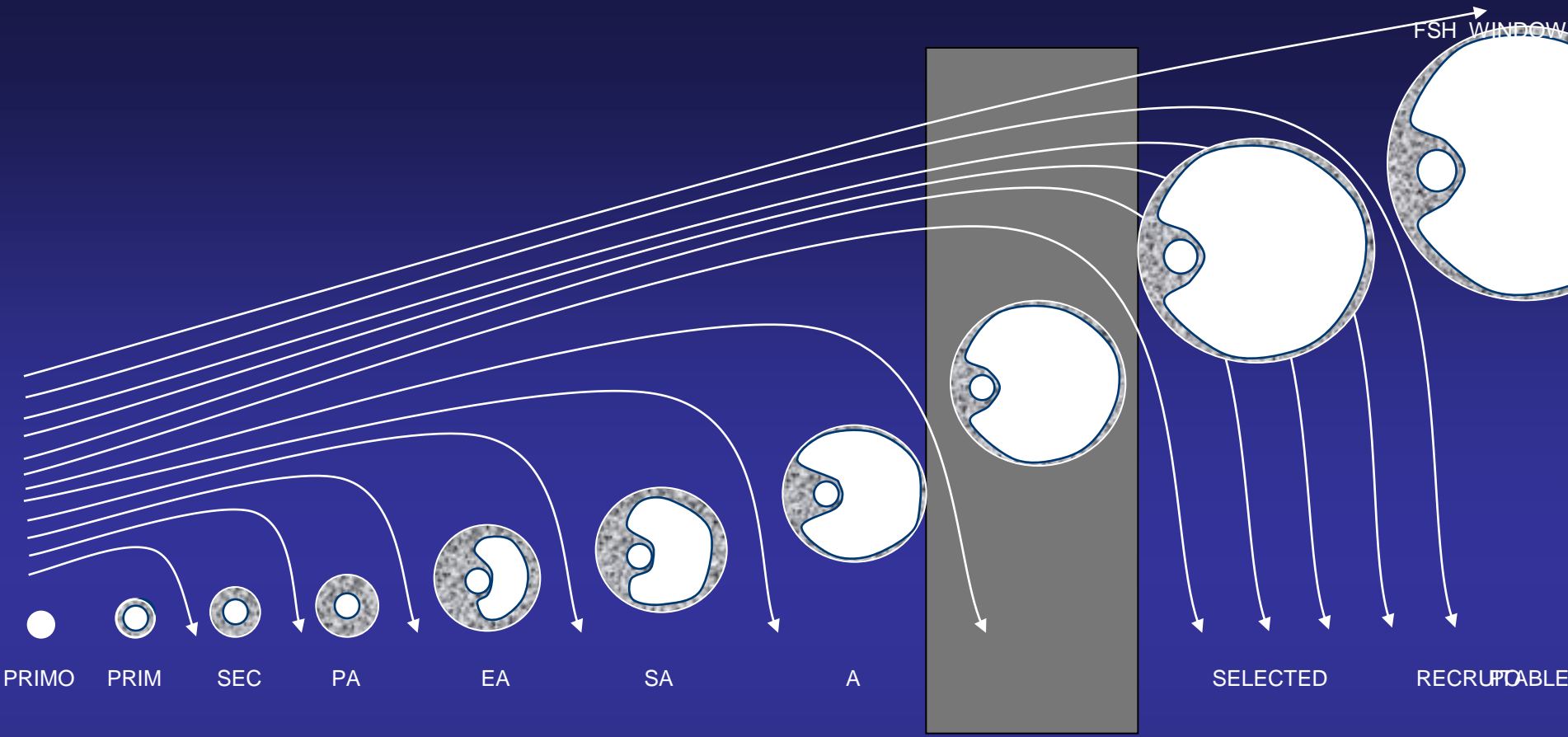


Hpg



Intraovarian modulators of follicular development

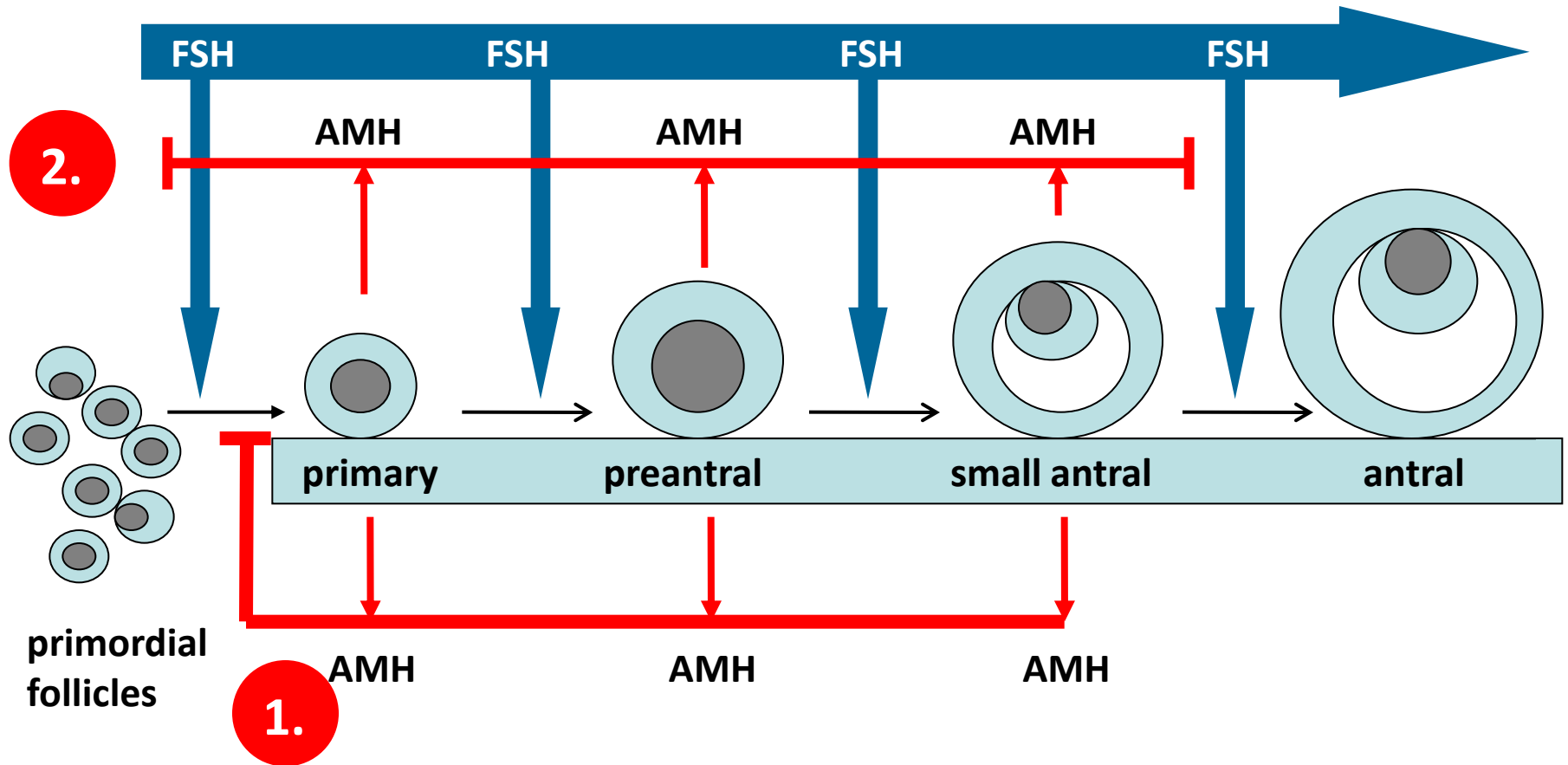
- IGF system
- Epidermal growth factor (EGF) system
- VEGF system
- Transforming growth factors ($TGF\alpha$, $TGF\beta$)
- Anti-Mullerian hormone (AMH)
- Bone Morphogenetic Protein (BMP-15) system



AMH

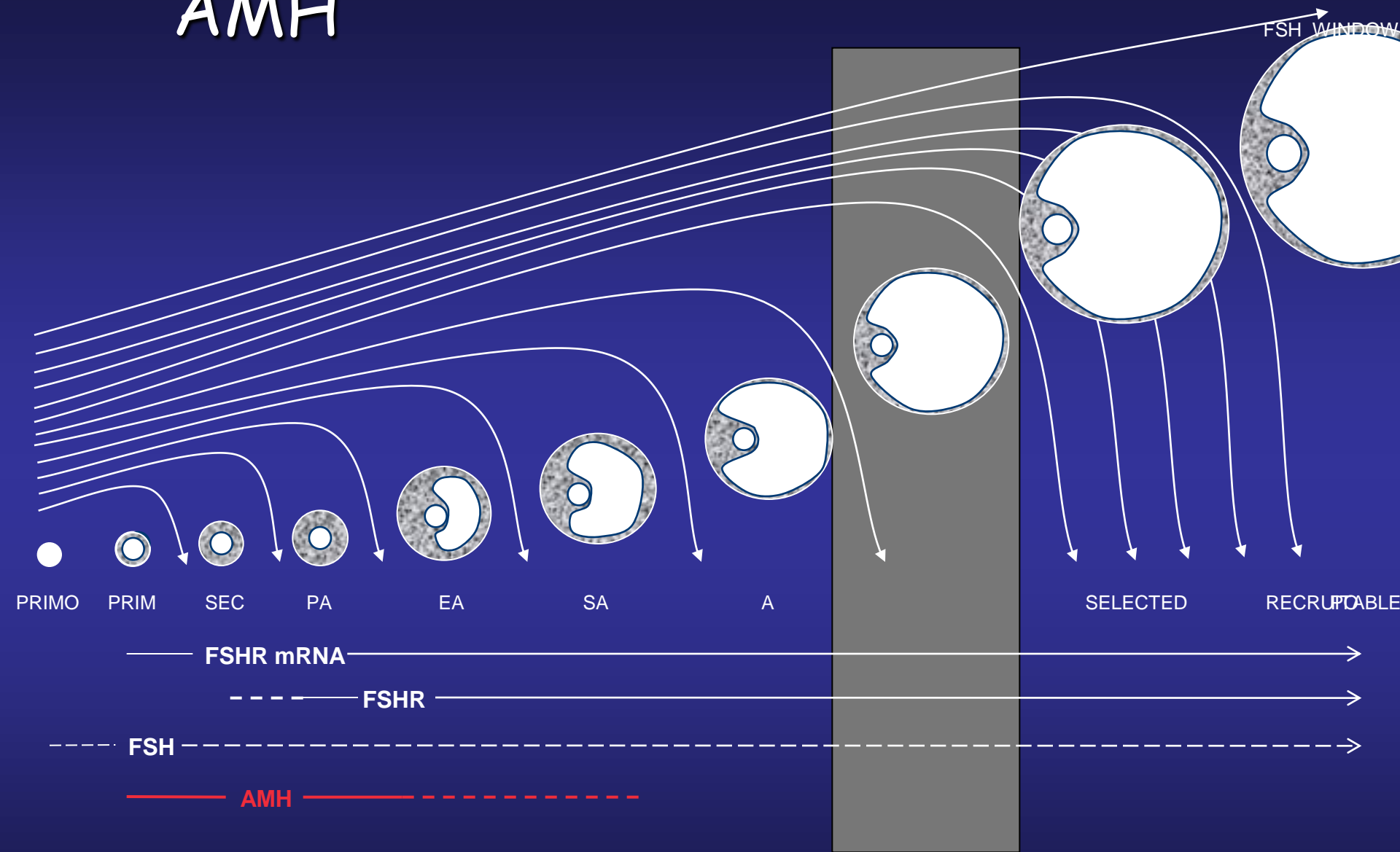
- AMH null mice:
 - Number of growing follicles are increased
 - > follicles more sensitive to FSH
 - Lower FSH levels
 - » Durlinger et al. 1999, 2001
- In vitro:
 - AMH inhibits FSH-dependent follicle growth (gc proliferation)
 - » Durlinger et al. 2001

Role of AMH in the ovary

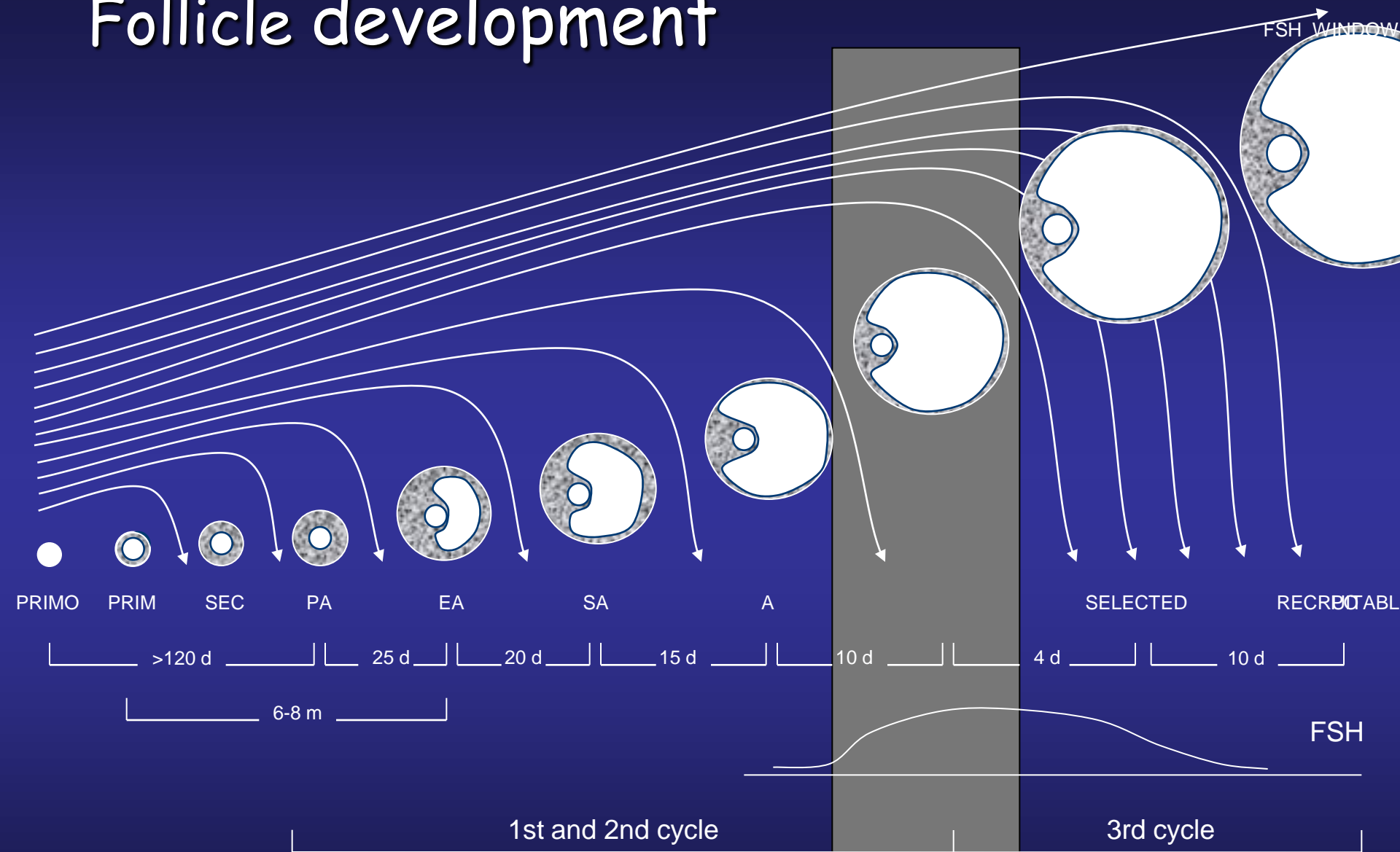


- 1) Inhibits recruitment of resting follicles
- 2) Inhibits the effect of FSH

AMH



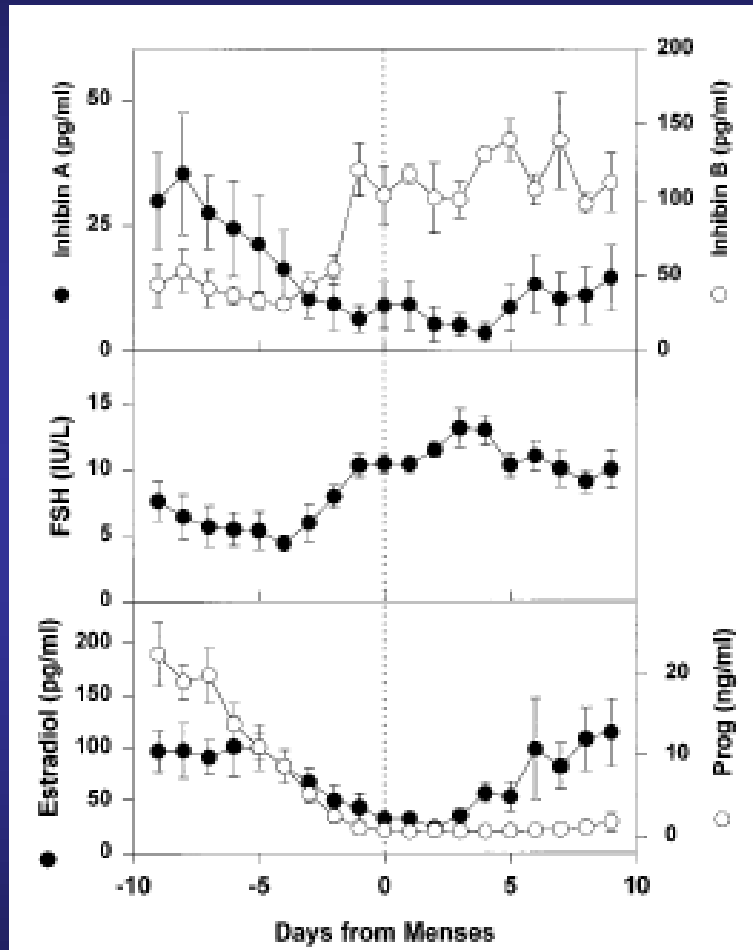
Follicle development



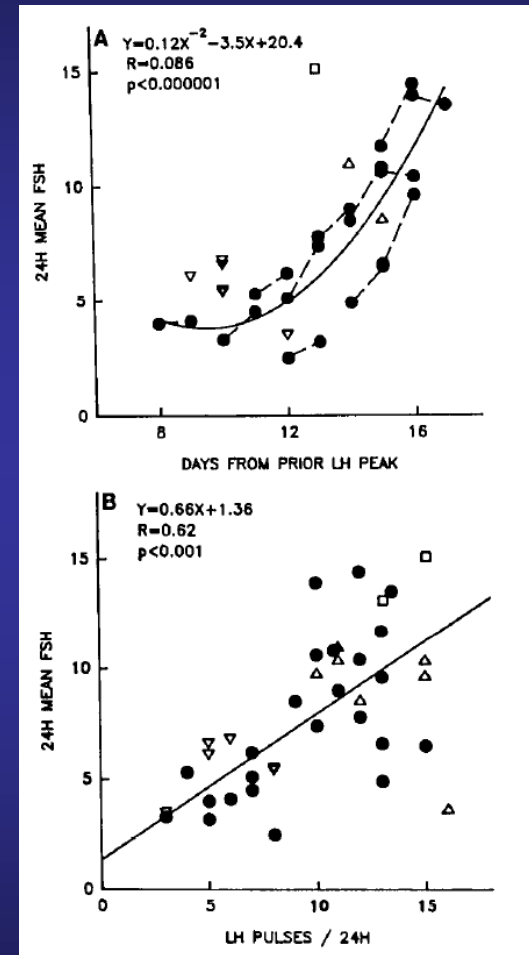
Luteal-follicular transition

- The rise in FSH is essential for recruitment of follicles into pool from which a dominant follicle is selected
- Increase in GnRH pulse frequency
- Close correlation between the rise in FSH and the increase in GnRH pulse frequency

FSH and FSH pulses during luteal-follicular transition



Welt et al. 1997



Hall et al. 1992

Selection of follicle cohort

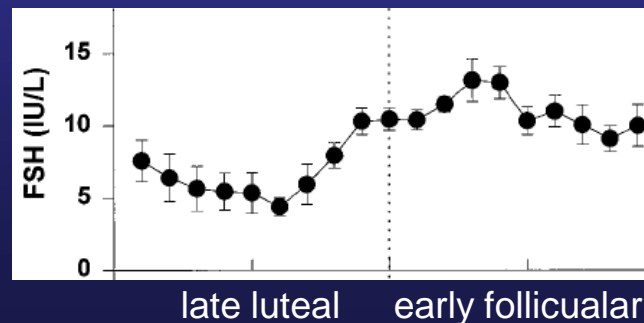
- Selection is critically dependent on the rise of FSH
- FSH give rise to continued growth of a limited number (cohort) of follicles
- Mechanisms by which FSH causes selection remains poorly understood

Cohort and dominance

- Some (largest) follicles more sensitive to FSH in late luteal phase
- Mitotic index of gc is important, and even smaller follicles can make up their growth delay in a few days
- In early follicular phase follicles with lower mitotic index are unable to make up the growth delay

Selection of dominant follicle

- The whole recruited cohort contributes to the initial decline in FSH levels during the first half of follicular phase
- The largest follicle has the major role in decreasing further FSH to levels below that required to support the growth of smaller follicles
- Estradiol and inhibin are the major factors produced by the selected cohort to suppress the secretion of FSH

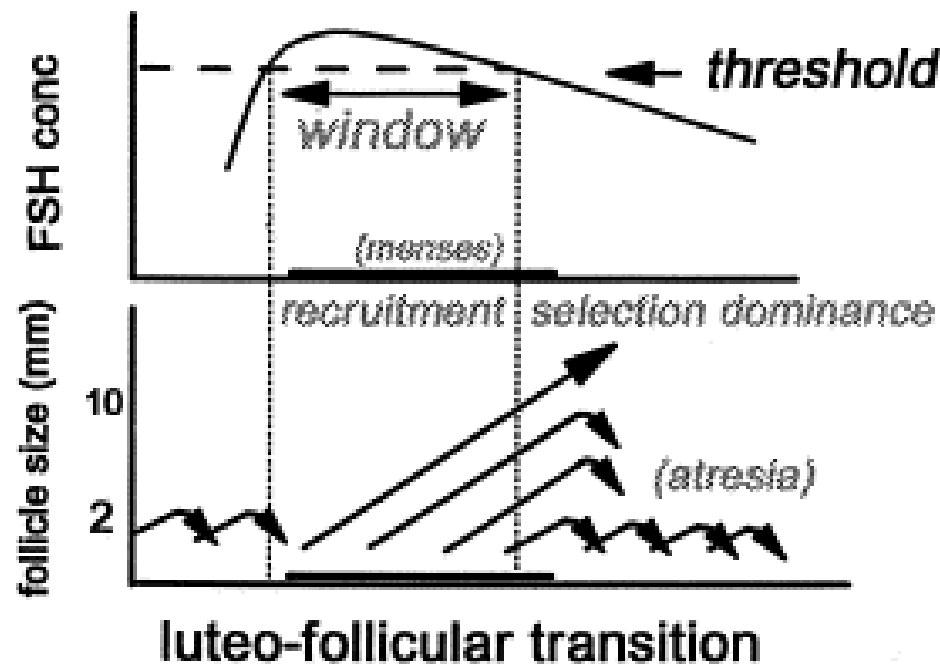


Dominant follicle

- In the human a single follicle from the cohort is selected
- Remaining follicles enter atresia
- GCs of dominant follicle become responsive to LH (induction of LHR by FSH) and less dependent on FSH

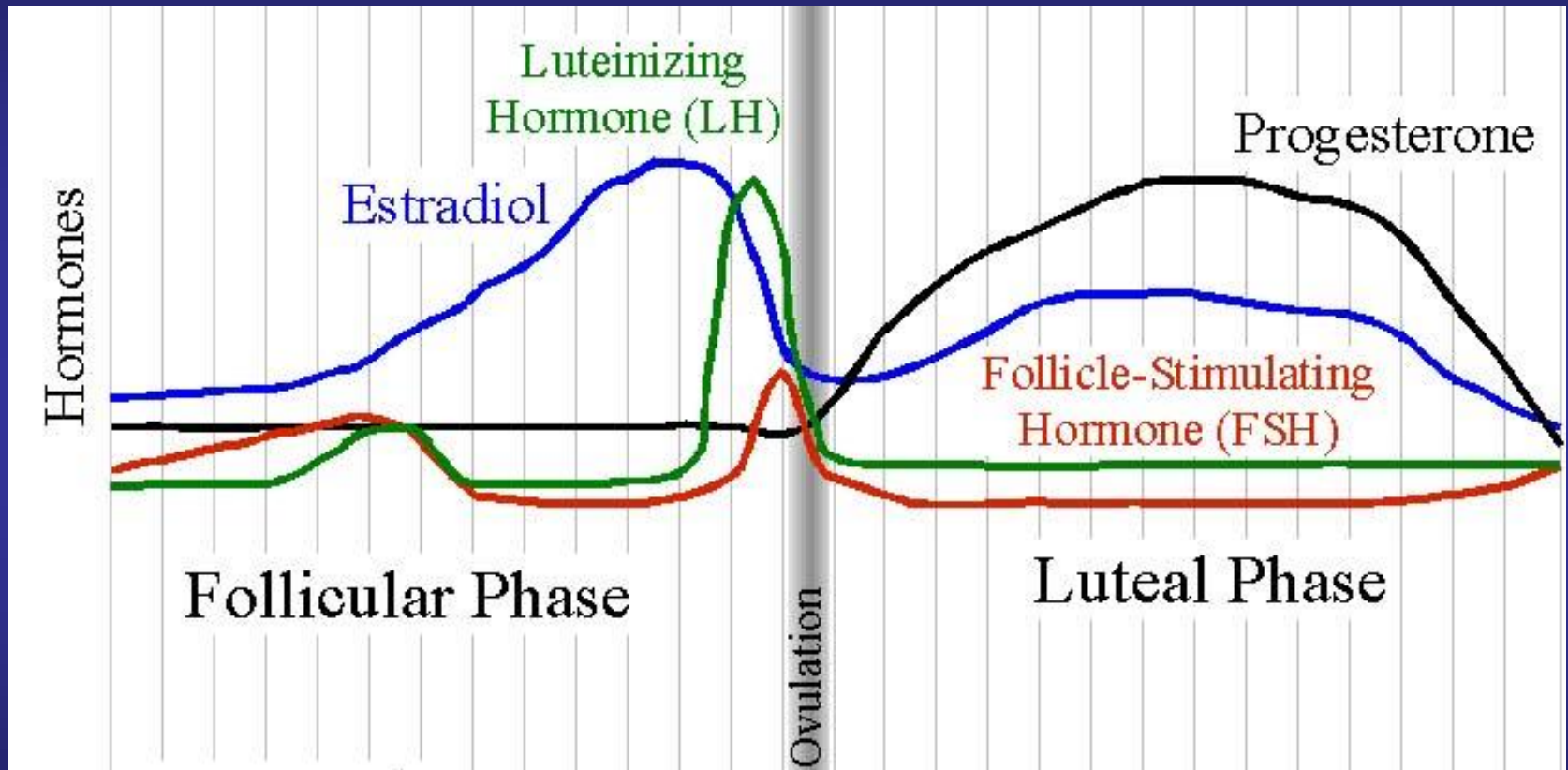
Human follicle development

- *FSH threshold/window concept* -

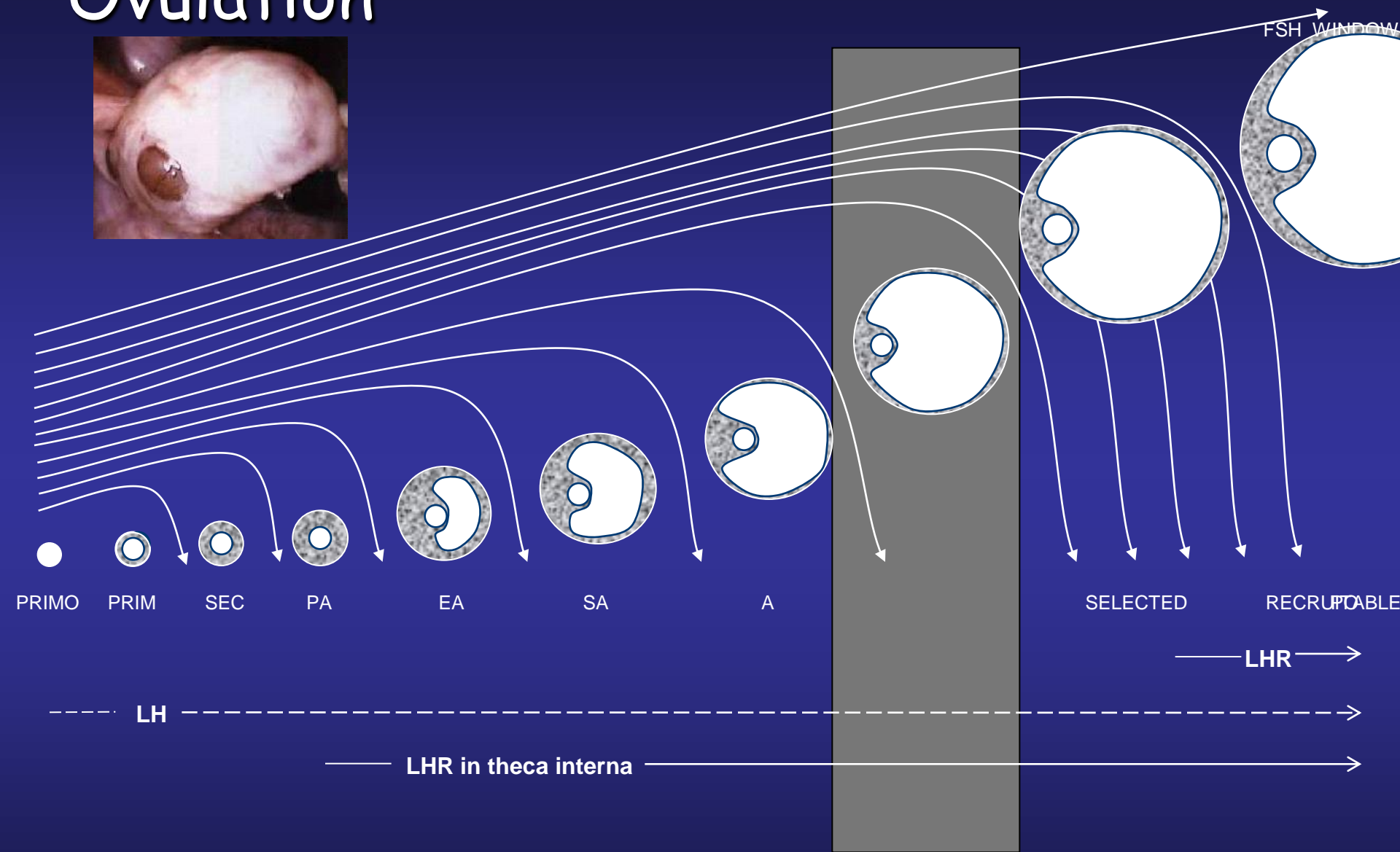


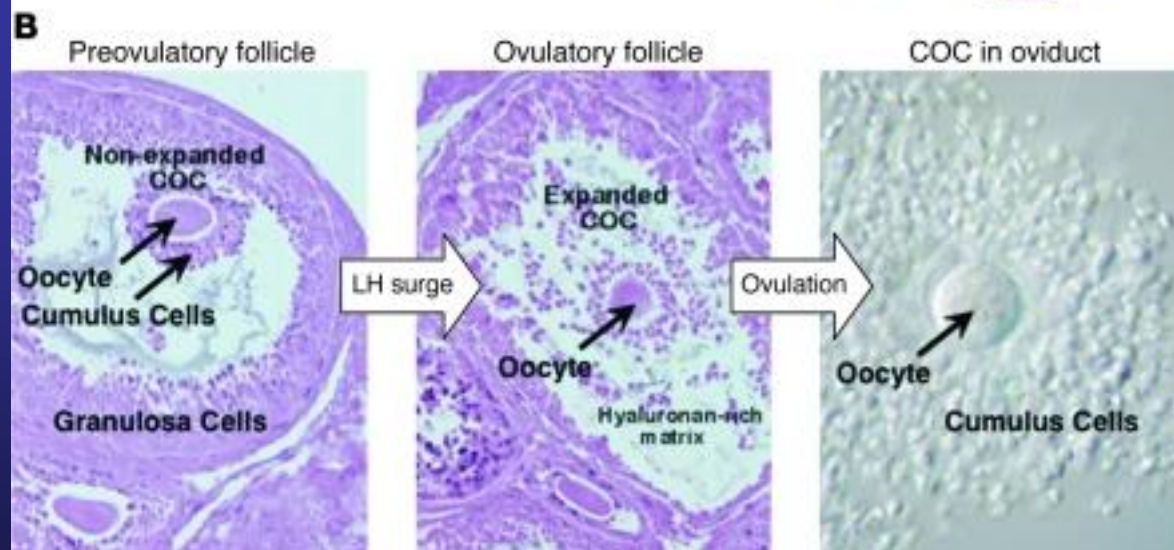
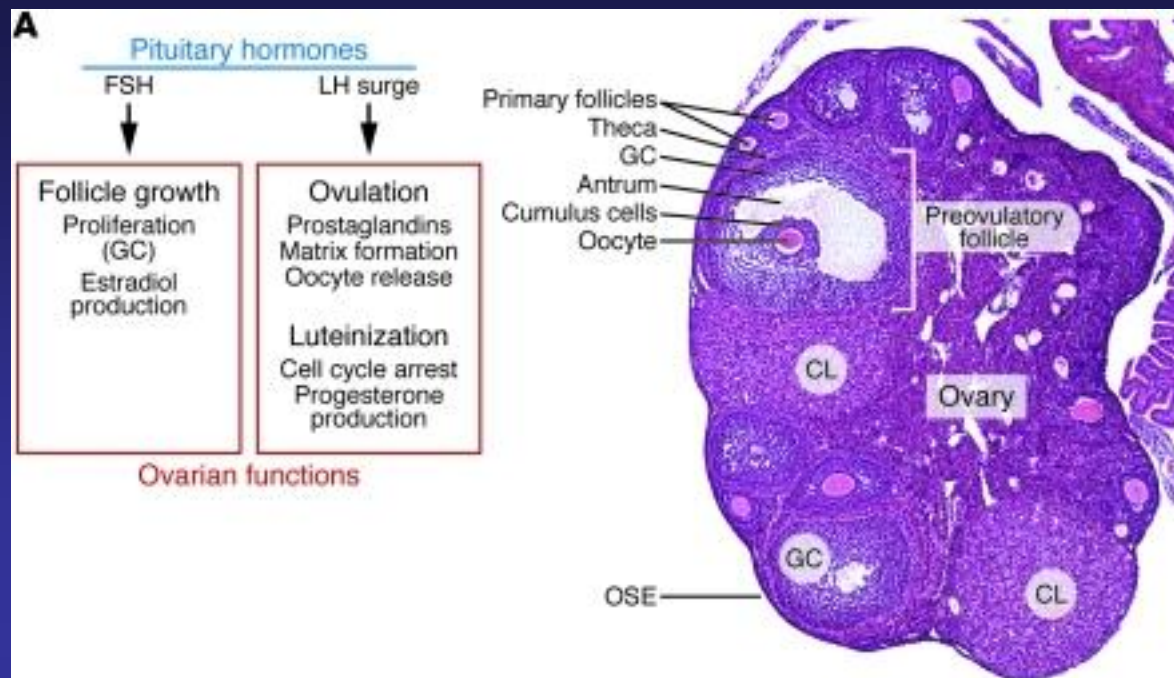
Adopted Fauser & Heusden 1997

Ovulation



Ovulation





Ovulation

- LH surge promotes terminal differentiation and oocyte maturation, required for ovulation of fertilizable egg
- LH directly stimulates TC and GC, but its effect on cumulus cells and oocyte are probably indirect
- Critical to LH-stimulated ovulation is the induction of EGF-like growth factors, which promote cumulus expansion and oocyte meiotic resumption
 - » Park et al. 2004, Panigone et al. 2008

Summary 1

- Gonadotropin dependence of follicular growth starts at preantral stage
- Follicle cells (gc, tc, oocyte) are responsive to gonadotropins already earlier
- Mechanisms by which FSH causes selection of follicle cohort remains poorly understood
- In addition to ovulation the expression of LHR (= constitutive low LH activity) is essential for follicular development from antral to preovulatory stage

Summary 2

- Intraovarian modulators (growth factors) participate in the regulation of gonadotropin-independent follicle growth but they are also involved in follicular maturation and follicle selection in later stages
- Animal studies indicate that especially BMP-system and EGF-like growth factors play important roles in development of dominant follicle(s) and ovulation
- The role these factors in follicle development and ovulation in human ovary is unknown and further investigations are needed